DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

ONCOLOGIC DRUGS ADVISORY COMMITTEE

65TH MEETING

Friday, March 17, 2000

8:05 a.m.

Holiday Inn Bethesda
Versailles I and II
8120 Wisconsin Avenue
Bethesda, Maryland

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C O N T E N T S

P R O C E E D I N G S

Call to Order and Opening Remarks

DR. SCHILSKY: Good morning. Welcome to day two of the ODAC meeting. I would like to begin by introducing the committee members. We have a number of new faces around the table this morning. Perhaps we can begin with Dr. Lippman.

Introduction of Committee

DR. LIPPMAN: Scott Lippman, M.D. Anderson, medical oncology.

MR. FLATAU: I am Arthur Flatau, patient representative.

DR. BLAYNEY: Douglas Blayney, medical oncologist, Los Angeles.

DR. NERENSTONE: Stacy Nerenstone, medical oncology, Hartford, Connecticut.

DR. KELSEN: David Kelsen, medical oncology, Sloan-Kettering, New York.

DR. PRZEPIORKA: Donna Przepiorka, medical oncology, Baylor, Houston.

DR. SIMON: Richard Simon, biostatistics, National Cancer Institute.

DR. BERMAN: Ellin Berman, Leukemia Service, Memorial Sloan-Kettering Cancer Center.

DR. SCHILSKY: Richard Schilsky, medical

oncologist, University of Chicago.

DR. TEMPLETON-SOMERS: Karen Somers, Executive Secretary to the Committee, FDA.

DR. SANTANA: Victor Santana, pediatric oncologist, St. Jude's Children's Research Hospital, Memphis, Tennessee.

DR. PELUSI: Jody Pelusi, oncology nurse practitioner in Phoenix, Arizona, and consumer rep.

DR. ALBAIN: Kathy Albain, medical oncology, Loyola University, Chicago.

DR. BEITZ: Julie Beitz, oncology, FDA.

DR. JUSTICE: Bob Justice, Deputy Division Director, FDA.

DR. PAZDUR: Richard Pazdur, Division Director, FDA.

DR. TEMPLE: Bob Temple, Office Director.

DR. SCHILSKY: Thank you.

Dr. Somers will read the Conflict of Interest Statement.

Conflict of Interest Statement

DR. TEMPLETON-SOMERS: The following announcement addresses the issue of conflict of interest with regard to this meeting and is made a part of the record to preclude even the appearance of such at this meeting.

Based on the submitted agenda for the meeting and

all financial interests reported by the participants, it has been determined that all interest in firms regulated by the Center for Drug Evaluation and Research which have been reported by the participants present no potential for a conflict of interest at this meeting with the following exceptions.

In accordance with 18 U.S.C. 208, full waivers have been granted to Dr. Richard Schilsky, Dr. David Kelsen, Dr. Scott Lippman, Dr. Victor Santana, Dr. Douglas Blayney, and Dr. George Sledge.

A copy of these waiver statements may be obtained by submitting a written request to the FDA's Freedom of Information Office, Room 12A-30 of the Parklawn Building.

Further, we would like to disclose that Dr. Kathy Albain and Dr. Richard Schilsky have involvements which do not constitute a financial interest in the particular matter within the meaning of 18 U.S.C. 208, but which may create the appearance of a conflict.

The Agency has determined notwithstanding these interests that the interests of the Government and the participation of Drs. Albain and Schilsky outweighs the appearance of a conflict. Therefore, they may participate fully in all matters concerning gemtuzumab ozogamicin.

In the event that the discussions involve any other products or firms not already on the agenda for which

an FDA participant has a financial interest, the participants are aware of the need to exclude themselves from such involvement, and their exclusion will be noted for the record.

With respect to all other participants, we ask in the interest of fairness that they address any current or previous involvement with any firm whose products they may wish to comment upon.

Thank you.

DR. SCHILSKY: Thank you.

Open Public Hearing

I have not been informed of anyone who wishes to address the committee during the open public hearing, but is there anyone in the audience who would like to address the committee?

[No response.]

DR. SCHILSKY: If not, I think we are prepared to move directly to the sponsor's presentation, so we will get started a little bit early.

NDA 21-174, gemtuzumab ozogamicin

Wyeth-Ayerst Laboratories

Sponsor Presentation

Introduction

MR. SICKELS: Good morning.

[Slide.]

My name is Barry Sickels with the Regulatory Affairs Department at Wyeth-Ayerst Research. On behalf of our organization, we are pleased to have this opportunity to review our NDA for gemtuzumab ozogamicin proposed for the treatment of CD33-positive acute myeloid leukemia in relapse.

During our presentation today, we will present data to support our position that gemtuzumab as a single agent is a novel, safe, and effective treatment for relapsed AML. I should add that there are currently no approved therapies in the U.S. specifically for treating relapsed AML.

[Slide.]

To begin, I would like to make a few opening remarks about gemtuzumab's unique structure, mechanism of action, and development history.

As depicted on this slide, gemtuzumab was also known as CMA-676 in clinical trials.

Gemtuzumab is the first in a class of compounds known as antibody-targeted chemotherapy.

Gemtuzumab has three components: a humanized recombinant antibody, hP67.6, targeted against the CD33 antigen, a derivative of the potent cytotoxic agent calicheamicin, which is an antitumor antibiotic, and a linker molecule connecting the antibody to the

calicheamicin.

The antibody portion of gemtuzumab binds specifically to the CD33 antigen on the surface of myeloid leukemia cells. The CD33 antigen is expressed on the surface of leukemic blasts in more than 80 percent of patients with AML. The antigen is also expressed by immature myeloid cells, and to a lesser degree by mature myeloid cells, but not by pluripotent stem cells.

After binding to the CD33 antigen, gemtuzumab is internalized, the calicheamicin released by hydrolysis, where it binds to DNA in the minor groove causing site-specific, double-strand breaks that ultimately result in the death of the leukemic cell.

We should point out that that monoclonal antibodies are ideally suited for the treatment of AML because of the accessibility of leukemic cells in the blood, bone marrow, spleen, and lymph nodes.

This is important because the leukemic cells of most AML patients express the CD33 antigen. Therefore a monoclonal antibody directed against CD33 offers a targeted delivery vehicle for a cytotoxic agent in this patient population.

In addition, because the CD33 antigen is expressed only on cells within the hemapoietic system, an agent like gemtuzumab that targets the CD33 expressing cells would be

expected to have an improved safety profile compared with that of conventional agents which are non-targeted and nonspecific.

[Slide.]

As we will demonstrate to you today, patients treated with gemtuzumab achieve remission with less severe mucositis, less severe infection, and less time in the hospital.

[Slide.]

I would like to turn briefly now to the regulatory history of gemtuzumab as presented on this slide.

We have had a highly interactive relationship with the FDA throughout the development of gemtuzumab. Some of the key interactions are highlighted on this slide.

The NDA was submitted on October 29, 1999 and received priority status designation by the FDA reflective of the seriousness of AML and the therapeutic potential of gemtuzumab in treating this disease.

Orphan drug designation was granted in November of 1999.

The significant agreements reached with the FDA during the development of gemtuzumab include the selection of clinical endpoints, the open-label, single agent design of the 201-U.S. study, and the format and content of the NDA.

[Slide.]

This slide depicts the NDA clinical database. The original NDA included data from 40 patients in our Phase I, dose-escalation study, and 104 patients from our three, Phase II studies.

The three, Phase II studies include Study 201, a U.S. study conducted in relapsed AML patients; Study 202-EU, conducted in Europe and similar in design to the 201 study, and Study 203, conducted in relapsed AML patients 60 years of age or greater.

The total Phase II database presented in our Advisory Committee background package, and which will be discussed by Wyeth-Ayerst here today, includes the original 104 NDA patients plus 38 patients included in the three-month update, for a total of 142 Phase II patients.

[Slide.]

We have the following agenda for today's meeting. Dr. Frederick Appelbaum of the Fred Hutchinson Cancer Research Center will present an overview of AML and the unmet medical need for therapies to treat this serious disease.

Dr. Mark Berger, Director of Clinical Research at Wyeth-Ayerst, will briefly discuss the pharmacokinetic data from our studies. Dr. Berger will also review efficacy and safety data from the three, Phase II studies conducted with

gemtuzumab.

Dr. Matthew Sherman, Assistant Vice President of Clinical Research at Wyeth-Ayerst, will review the risk/benefit of gemtuzumab and discuss its utility in the clinical setting. Dr. Sherman will also present the overall conclusions.

[Slide.]

To conclude, gemtuzumab is a novel, safe, and effective therapy proposed for use in the treatment of CD33-positive acute myeloid leukemia in relapse. The recommended dose is 9 mg/m^2 administered as a two-hour intravenous infusion.

The recommended treatment course is a total of 2 doses given 14 days apart. As we will demonstrate to you today, patients treated with gemtuzumab as a single agent achieve remission with an improved safety profile in terms of severe mucositis and severe infection. This results in a reduced need for hospitalization in patients treated with gemtuzumab.

Again, as I noted earlier, there are currently no approved therapies in the U.S. specifically for treating relapsed AML. We believe that gemtuzumab will satisfy an important unmet medical need in this seriously ill patient population.

At this time, I would turn the podium over to Dr.

Appelbaum who will present an overview of AML.

Overview of Acute Myeloid Leukemia

DR. APPELBAUM: Thank you, Barry.

[Slide.]

This year, approximately 10,000 Americans will develop acute myeloid leukemia. Their median age will be slightly above 60 years, and the majority of them will achieve an initial complete remission with combination chemotherapy.

However, despite receiving state-of-the-art consolidation chemotherapy, the vast majority of these patients will relapse with their disease. At least 60 percent of patients who are under age 50 and more than 80 percent of patients over age 50 will develop recurrent leukemia, usually within two years of diagnosis.

[Slide.]

The goals of treatment of patients after relapse depend in part upon the patient's particular situation, so that for younger patients who may be candidates for hematopoietic stem cell transplantation, it is important to be able to achieve a second remission in order to provide the time necessary to arrange the transplant and also to improve the outcome of the transplant.

It is also, of course, obviously important while trying to reinduce patients to avoid severe toxicities which

would preclude or at least prejudice the outcome of a subsequent transplant.

One reason to reinduce patients with AML before proceeding to a transplant, as I said, is the very practical issue of providing time to get the patient to the transplant. Even in the very best of circumstances, where a patient has a HLA identical sibling available to carry out the transplant, it often takes several weeks in order to find a transplant bed, settle insurance issues, transfer the patient, and initiate the procedure.

In those circumstances where one is relying on an unrelated donor, it may require three to four months in order to identify the donor and make the arrangements necessary to initiate the transplant.

A second reason to reinduce patients before proceeding to transplantation is to improve the outcome of the procedure.

[Slide.]

Shown here are the results of unrelated donor transplants for recurrent AML at the Fred Hutchinson Cancer Research Center. Virtually no patients turn out to be long-term survivors if they are transplanted in frank relapse with circulating blasts, whereas, approximately 30 percent of patients turn out to be long-term survivors if transplanted in second remission.

[Slide.]

The goals of treatment for patients who are not transplant candidates are somewhat different. There are occasional patients who achieve long-lasting second remissions following re-treatment with aggressive combination chemotherapy regimens.

In most studies, these patients are characterized as being young, with favorable cytogenetics, and having had a first remission of particularly long duration. Unfortunately, these patients represent only a handful of patients with recurrent AML, and the vast majority of patients cannot expect that sort of favorable outcome.

For the majority of patients with recurrent AML, the goals of treatment are unfortunately modest. Even with successful reinduction therapy, expected survival is only measured in months, and so the goals of therapy are short-term prolongation of life and palliation of symptoms.

[Slide.]

Although a considerable number of different single agents and combination regimens have been tested as reinduction therapy in AML, none has emerged as being clearly superior. Thus, there is no generally accepted standard of care for such patients.

Reported remission rates range from 10 to 70 percent, with the results at these two extremes limited to

very small, non-controlled studies. Complete response rates in larger studies generally range between 30 and 50 percent.

The average duration of remissions ranges from five to nine months, and fewer than 10 percent of patients can be expected to be alive at three years.

Shown here are two contemporary representative studies. The MRC AML-R study has only been reported in abstract form, but the complete results have been made available to us by Dr. Alan Burnett.

This study reports a complete response rate of 43 percent, a median duration of remission of six months, and approximately 8 percent of patients alive at three years.

A recently published SWOG study comparing high-dose ara-C with high-dose ara-C plus mitoxantrone reported a complete response rate of 38 percent, a median duration of response of seven months and approximately 10 percent of patients alive at three years.

The regimens in both of these studies were associated with substantial toxicities. These patients were treated with high-dose ara-C-containing regimens, and they become quite ill. The vast majority of them have--of course, all of them have pancytopenia, the vast majority of them develop mucositis, and infection is seen again in the majority of patients, and others will develop severe hepatic, renal, and a particularly disabling form of

cerebellar toxicity in some.

The treatment-associated mortality rates in these two studies were 15 and 21 percent respectively, despite being carried out in patients whose median age was less than 50 years.

As pointed out in the extensive literature review conducted by Wyeth-Ayerst Research and included in the submission packet to the FDA, the range of response rates in AML reinduction studies is quite wide.

Results at the extremes have been restricted to small, nonrandomized trials, and it is the opinion of many experts in leukemia that a great deal of the heterogeneity in outcome among other studies can be explained at least in part by variability in patient selection, their prior therapy, and response definitions.

[Slide.]

The importance of patient treatment characteristics on outcome is becoming increasingly appreciated, and this is particularly significant when one realizes how selective some of these reports can be. For example, the MRC study, approximately 22 percent of patients who were eligible for trial, were not entered onto the study and were treated instead with palliative therapy only.

The most important established predictors of outcome are duration of first remission and age. Although

data are less complete, disease cytogenetics, known to be a powerful predictor in predicting the outcome of initial induction, also seems to predict outcome for relapse patients.

Over time, the form of therapy that patients have previously been exposed to has changed. For example, the initial trials of high-dose ara-C were largely carried out in patients who had never been exposed to that regimen before, whereas currently the vast majority of patients receive multiple cycles of high-dose ara-C as part of induction or consolidation.

Finally, the definitions of complete response vary from study to study. For example, some studies require recovery of neutrophils to only 1,000, and others, such as the MRC, have no platelet recovery requirement in their definition of CR.

[Slide.]

Shown here are results provided to us by Eli Estey from M.D. Anderson demonstrating the importance of the duration of first remission on the likelihood of successful reinduction therapy.

Among the few patients with first remissions longer than two years, there was a 73 percent reinduction rate. However, these patients represent less than 10 percent of the patients seen at M.D. Anderson over the

period of this study.

The reinduction rate, however, for patients who have a first remission of less than one year was only 14 percent, and these patients obviously represent the larger percentage of patients that were seen at M.D. Anderson over this period.

[Slide.]

The association of age with outcome is shown in the MRC-AML-R trial where patients who were less than age 55 had a 58 percent complete response rate, whereas the complete response rate was only 37 percent for those patients who were over age 55.

It is worth remembering again that the average age at diagnosis of AML is over 60, and so the majority of patients do fall into this category.

[Slide.]

In summary then to this point, the majority of patients with AML will relapse after initial therapy. There is no generally accepted therapy for reinduction. Among the combination regimens that have been reported, the remission rates have varied widely, but average between 30 and 50 percent, the remission durations have been short, and the variability in outcome is likely due, at least in part, to variability in the patients studied, their prior therapy, and differing definitions of response.

Finally, all of these regimens have been associated with considerable toxicity. These observations emphasize the need for more effective, less toxic therapy for this difficult group of patients.

[Slide.]

During the normal course of myeloid differentiation, a number of surface antigens appear and disappear in a predictable and orderly manner. One such surface antigen is CD33.

This antigen has a molecular weight of 67 kd and is expressed on the leukemic blasts in from 80 to 90 percent of cases of AML. The presence of CD33 is not of prognostic significance in the treatment of AML, however,

The antigen is not present on the pluripotent hematopoietic stem cell and is absent on essentially all non-hematopoietic tissues. Each leukemic cell expresses approximately 10,000 copies of the antigen on the cell surface, and after antibody binding the antigen-antibody complex is rapidly internalized.

[Slide.]

The pluripotent stem cell does not express CD33, but does express CD34. With commitment to the myeloid, the erythroid, or the megakaryocytic lineage, CD33 begins to be expressed.

Because the stem cell does not express CD33, but

leukemic cells do, and because after antibody binding, the antibody-antigen complex is rapidly internalized, CD33 appeared to many of us to be an obvious target for an antibody-directed chemotherapeutic approach.

This concept was reinforced by experiments performed in the laboratory of Dr. Irwin Bernstein who studied the effects of in vitro treatment of AML marrow with an anti-CD33 antibody plus complement using G6PD as a marker of clonality.

Dr. Bernstein found that prior to treatment, as expected, everything that grew out in the dish was from the malignant clone. However, in a proportion of cases, following treatment with the anti-CD33 antibody and elimination of the CD33-positive cells, there was outgrowth of normal nonclonal hematopoiesis from the CD34 normal hematopoietic stem cell, suggesting that removal of CD33-bearing AML allows regrowth of normal hematopoietic stem cells.

These observations led to the development of gemtuzumab ozogamicin, the agent we are discussing today. It was our hope that by targeting a potent cytotoxic agent to CD33, a powerful anti-leukemic therapy with an excellent safety profile would result.

Having used this drug in the clinic myself, I can tell you that it is clear to me that this goal has been

largely achieved. Gemtuzumab ozogamicin is not a perfect agent, however. There are infusional side effects and the leukemia of many patients does not respond completely to the drug.

However, even as a single agent, it is able to induce important clinical responses in approximately 30 percent of patients with recurrent AML, and it does so with far fewer side effects than are seen with conventional high dose regimens. This agent is a useful tool for the treatment of recurrent AML and many patients will benefit from it.

Thank you.

I would now like to introduce Dr. Mark Berger, Director of Clinical Research at Wyeth-Ayerst.

Mark.

Design of Clinical Studies

Efficacy and Safety Results

DR. BERGER: Thank you, Dr. Appelbaum, and good morning.

[Slide.]

We are pleased to present information today on gemtuzumab ozogamicin, the first antibody-targeted chemotherapy agent. Our data demonstrate that targeting the delivery of calicheamicin, a potent cytotoxic drug, with an antibody against CD33 results in a decrease in many of the

severe side effects usually associated with the treatment of acute myeloid leukemia in relapse, and leads to a decreased duration of hospitalization during therapy.

The results from our three, Phase II studies also show that the efficacy of gemtuzumab as a single agent is comparable to that of combination regimens used for the treatment of relapsed AML.

[Slide.]

A total of 195 patients were enrolled in the gemtuzumab clinical program. Our adult Phase I study enrolled 40 patients with relapsed and refractory AML, and three, Phase II studies have enrolled 142 patients.

We also have a pediatric Phase I study and a compassionate use study, which had only enrolled a small number of patients at the time of data cut-off for our application.

[Slide.]

The results of the Phase I study were used to plan the dosing schedule for the Phase II clinical trials. Because the activity of gemtuzumab is dependent on CD33 expression, patients with relapsed and refractory AML enrolled in the open-label Phase I trial all had CD33-positive AML blasts as determined by flow cytometry.

Doses studied ranged from 0.25 to 9 mg/m^2, with a minimum of 3 patients in each dosage group. Gemtuzumab was

administered as a two-hour intravenous infusion every 14 days for up to 3 doses.

[Slide.]

The highest dose evaluated, 9 mg/m^2, was selected for the Phase II clinical trials. This dose was associated with acceptable safety with clinical responses, and with consistent CD33 site saturation.

[Slide.]

Speaking first of safety, in the Phase I study the most common nonhematologic adverse events were infusion-related adverse events, which were similar to those seen after the administration of other antibody-based products.

These included transient fever, chills, and, less frequently, hypotension, occurring shortly after the end of the gemtuzumab infusion and lasting for several hours. The infusion-related events occurred despite the prophylactic use of one dose of acetaminophen and one dose of antihistamine just before gemtuzumab administration.

The complete lack of severe mucositis suggested that antibody-targeted chemotherapy might have a favorable adverse event profile.

Because CD33 is expressed on normal hematopoietic progenitor cells, myelosuppression was expected, and, indeed, significant myelosuppression was observed. Delayed recovery of platelets compared to neutrophils occurred in

two patients who had bone marrow blast clearance at the dose of 9 mg/m^2.

In general, for patients with bone marrow blast clearance the length of severe neutropenia was less than five weeks after the last dose of gemtuzumab. However, one patient with blast clearance experienced six weeks of severe neutropenia after three doses of 9 mg/m^2. We therefore decided to use two, 9 mg/m^2 doses in the Phase II studies.

[Slide.]

Efficacy results also supported the choice of 9 mg/m^2 for the Phase II dose. Following gemtuzumab monotherapy, 2 of the 40 patients enrolled in the Phase I study achieved a complete remission with full recovery of blood counts. These patients were in the 1 and 4 mg/m^2 dosage groups.

In addition, 7 other patients, including 4 patients at 9 mg/m^2, had clearance of bone marrow blasts for varying periods of time. These results suggested that gemtuzumab may be an effective agent in patients with relapsed AML.

[Slide.]

Finally, CD33 site saturation data also supported the selection of 9 mg/m^2 as the dose for the Phase II studies. Since gemtuzumab is a delivery system for calicheamicin, saturation of CD33 sites is necessary for

efficacy.

This slide shows the peak CD33 saturation after the first dose. Each bar indicates one patient in each of the dosage groups, and represents the maximum saturation after the first dose. Saturation of CD33 sites on peripheral white blood cells was consistently above 80 percent in the 9 mg/m^2 dosage group.

Patients with complete remission, the magenta bars, or bone marrow blast clearance, the yellow bars, had saturation of at least 79 percent of CD33 sites after the first dose, suggesting that this level of CD33 saturation is necessary, but not sufficient, to obtain a response.

[Slide.]

In addition, the persistence of peak levels of CD33 site saturation at 9 mg/m^2 was superior to that at other dose levels. The y axis on this chart shows the percent of CD33 saturation, with time in hours on the x axis.

At 9 mg/m^2, the dose shown here by the magenta line at the top, peak levels of CD33 site saturation were maintained more effectively for the first 24 hours than at other doses. Therefore, 9 mg/m^2 appeared to be an appropriate dose to utilize in Phase II clinical trials based on the safety profile, on clinical responses, and on consistent CD33 site saturation.

[Slide.]

Additional information on an appropriate dose schedule was obtained from pharmacokinetic studies. hP67.6, which is the antibody portion of gemtuzumab, makes up 97 percent of the drug, and is the best surrogate for the overall pharmacokinetics of gemtuzumab.

Following the first dose, the pharmacokinetic parameters of hP67.6 were: a peak plasma concentration of 3.1 mg/L, an AUC of 132 mg hours per liter, and a half-life of 67 hours. With this half-life, accumulation of gemtuzumab is not anticipated using a dose schedule with a 14-day period between doses.

[Slide.]

We studied the pharmacokinetics of total calicheamicin and free calicheamicin, as well, and determined that their pharmacokinetic profile tracked that of hP67.6. The yellow curve here shows the concentration of hP67.6 after the first dose of gemtuzumab, with a maximum concentration shortly after the end of the gemtuzumab infusion.

The curve for total calicheamicin concentrations, shown here in blue, paralleled the same time course as that for hP67.6, but at a concentration more than 1 log lower, indicating that gemtuzumab remains intact in the circulation.

Free calicheamicin concentrations were very low, which was important as the calicheamicins have been shown to be potent toxins in animal studies. As you can see from the red triangles, free calicheamicin levels were below 0.01 mg/L at all times, and were only above the limit of detection for several hours after gemtuzumab administration.

[Slide.]

Now we will turn our attention to the Phase II studies. The objectives of the Phase II studies were, first, to determine the remission rate following gemtuzumab therapy in patients with CD33-positive AML in first relapse. And, second, to evaluate the safety of two, 9 mg/m^2 doses of targeted therapy with gemtuzumab.

[Slide.]

As mentioned previously, there were three, Phase II studies conducted in North America and in Europe. Study 201 enrolled 65 patients in the United States and Canada. Study 202 enrolled 40 patients in eight European countries, and Study 203 enrolled 37 patients in the U.S. and in five European countries.

[Slide.]

All patients enrolled in the Phase II studies had AML in first relapse as documented by bone marrow evaluation and confirmed by the central flow laboratory. There were only minor differences between the three studies. For

instance, Study 203 enrolled only patients 60 years of age and older, and allowed patients with durations for first remission of as little as three months to be entered.

[Slide.]

There were several other major eligibility requirements. Hydroxyurea was utilized to lower peripheral white blood cell counts to less than 30,000 prior to the start of therapy. Patients with secondary AML, and those with myelodysplastic syndrome preceding their initial AML presentation, were excluded as were patients with prior hematopoietic stem cell transplantation. An exception was made to include patients with prior HSCT in Study 202 to facilitate enrollment. However, only 5 of the 40 patients enrolled in that study had prior HSCT.

[Slide.]

Targeted therapy with gemtuzumab depends on the presence of CD33 on the surface of the leukemia cells, and documentation of CD33 expression was required for entry into each of the Phase II studies.

CD33 expression was evaluated by two cross-validated central facilities, one in the United States and one in Europe. Both utilized the same anti-CD33 monoclonal antibody as the primary antibody for evaluating CD33 expression. This antibody was later humanized to produce gemtuzumab.

The criteria for evaluating CD33 expression were based on the findings in the responders in the Phase I study. These criteria were, first, that the fluorescence of labeled blast cells had to be 4 times the autofluorescence of the unstained blast cells. In addition, 80 percent of the labeled cells had to be positively staining, that is, above the level of virtually all the unstained cells.

[Slide.]

Let's turn to the design of the Phase II studies. All patients received 9 mg/m^2 of gemtuzumab as a single agent given as a two-hour intravenous infusion. Gemtuzumab was administered to outpatients, in contrast to many common AML treatments that require inpatient hospitalization for continuous intravenous infusions.

To prevent infusion-related adverse events, patients were premedicated with acetaminophen and an antihistamine, and received two additional doses of acetaminophen after gemtuzumab administration.

Patients were planned to receive two doses 14 days apart although if disease progression occurred after dose 1, dose 2 was not administered. A third dose could be given if a bone marrow examination after the second dose demonstrated residual leukemia and adequate cellularity. The second and third doses were given regardless of neutrophil and platelet counts, which were expected to be markedly decreased.

Twenty-eight days after receiving the last dose of gemtuzumab, patients had a bone marrow aspirate and biopsy and were then evaluable for response. This bone marrow exam marked the end of the treatment period and the start of the follow-up period.

[Slide.]

During the follow-up period, all patients were evaluated monthly for six months and then every three months with data collection at that time limited to information on disease status and survival. Patients were followed until death or until the date of data cut-off. During the follow-up period, additional post-remission therapy, as noted on the slide, was permitted.

[Slide.]

All patients who had less than 5 percent blasts in their bone marrow aspirate or biopsy at the bone marrow exam performed at the end of the treatment period were eligible to become remission patients. To do so, they had to have recovery of peripheral blood counts to predetermined levels while they were transfusion independent. The specific requirements for remission will be discussed shortly.

Efficacy results were based on the evaluation of bone marrow aspirates and biopsies by an independent expert pathologist, Dr. John Bennett, Professor of Medicine, Pathology and Laboratory Medicine at the University of

Rochester School of Medicine.

Dr. Bennett was blinded to the patient's identity, clinical site, and remission status, as well as to the sequence and time of the patient's bone marrow slides.

[Slide.]

The age range of patients enrolled in the three, Phase II studies was similar to that of all patients with AML. The median age of all AML patients is approximately 62 to 65, while in our studies, 142 patients had a median age of 61 years, with the youngest patient being 22 and the oldest being 84.

There were 59 percent males and 41 percent females, and the patients were predominantly white, with only 6 percent non-white patients. The median duration of first remission was 11.1 months. Although patients with a duration of first remission of less than three months were allowed in Study 203, there were only 14 patients with a first remission duration of three to six months who were entered in that study.

[Slide.]

Patient enrolled in the study had received aggressive therapy prior to relapse. A high percentage of patients, 94 percent, has received postremission therapy during first remission, and 70 percent of the patients had previously received high-dose ara-C.

Although not all patients had cytogenetic evaluation at relapse, only 5 percent of those that did were in a favorable category. Baseline hematologic values, shown here, are appropriate for patients with relapsed leukemia.

[Slide.]

Based on results from the Phase I study, two categories of remission were identified: CR for complete remission, and CRp for complete remission with incomplete platelet recovery.

Patients with CR were characterized as having no peripheral blasts and bone marrow blasts less than or equal to 5 percent, with hemoglobin greater than or equal to 9, an ANC greater than or equal to 1,500, and a platelet count greater than or equal to 100,000.

These blood counts had to be obtained when the patients were independent of red blood cell and platelet transfusions. The criteria for CRp were exactly the same, except that patients had platelet counts that were less than 100,000. As our data will show, CRp patients were comparable to CR patients in all efficacy measures.

We will also utilize the term OR, for overall remission, to refer to CR and CRp patients combined, and the term NR, for non-responder, for patients who did not achieve remission.

[Slide.]

We will now turn to an evaluation of our efficacy data. The overall remission rate in all 142 patients was 30 percent. Sixteen percent of patients met the criteria for CR and 13 percent met the criteria for CRp.

The rates of remission were similar in the 201 and 202 studies. Patients in the 203 study were older and had a shorter duration of first remission, and, as a result, the lower remission rate in that study was not unexpected.

As we will show shortly, the overall remission rate of 30 percent with gemtuzumab as a single agent is comparable to results reported in the literature with combination therapies.

[Slide.]

Patients who achieved remission and those who did not were similar in factors considered to be major prognostic factors. For instance, the 42 overall remission patients and the 100 non-responder patients were similar in median age, in median duration of first remission, and in the percent of patients who received postremission therapy in first remission.

Now we will look at remission rates in subsets of patients divided by age and by duration of first remission.

[Slide.]

Studies in patients with relapsed AML have shown a lower remission rate in older patients and in patients with

shorter durations of first remission.

While there are small variations in remission rates, our data show that gemtuzumab has significant efficacy in patients 60 years of age and older, and in patients with durations of first remission of less than 12 months.

[Slide.]

With one exception in the upper right-hand corner, the overall remission rate was essentially the same for subsets of patients with differing ages and durations of first remission. Patients who were 60 years of age or older with a duration of first remission of less than 12 months had a lower remission rate, as would be expected based on results with other treatment regimens.

[Slide.]

Now we will turn to an evaluation of the data on patient survival. This slide shows the overall survival of all 142 patients in the three, Phase II studies.

Median duration of overall survival was 5.9 months from the first dose of gemtuzumab. The probability of surviving beyond one year was 31 percent. As we will show shortly, a 31 percent one-year survival is comparable to results with conventional regimens.

Of the 16 patients followed for at least one year, 13 are still alive.

[Slide.]

Relapse-free survival of CR and CRp patients was comparable. Relapse-free survival was measured from the date that CR or CRp was reached until the time of relapse, death, or the date of data cut-off.

The results of the log-rank test show that the relapse-free survival curves for the CR and CRp patients were similar. For the total of 42 overall remission patients, the median relapse-free survival was 6.8 months.

[Slide.]

As Dr. Appelbaum explained, although obtaining remission is a decisive achievement, patients who then undergo hematopoietic stem cell transplantation have a much improved chance for long-term survival.

Although the number of patients in each group are small, patients with CR and CRp had a similar rate of transplantation, whereas the rate of transplantation for non-responder patients was significantly lower.

Not all remission patients were considered candidates for transplant; some patients received combination chemotherapy during remission and some patients received no further therapy.

[Slide.]

Patients with CR and CRp differed from non-responders both in the rate of hematopoietic stem cell

transplantation, as well as in the results after transplant. Patients with CR and CRp had similar rates of survival 100 days after transplantation, whereas the rate of survival of non-responder patients after transplant was significantly lower.

Median relapse-free survival after transplantation had not been reached for CR or for CRp patients. Median overall survival had not been reached for any of the three groups, although the present data suggest that non-responder patients do not survive as long as CR or CRp patients.

[Slide.]

The data we have shown demonstrates that CR patients are clinically comparable to CRp patients in terms of efficacy as measured by relapse-free survival and outcome after transplantation. We conclude that CR and CRp can be combined together in an OR, overall remission, rate to measure the effectiveness of gemtuzumab therapy.

[Slide.]

There is no standard therapy for patients with AML in first relapse, which is one of the main reasons that the gemtuzumab studies were performed without a comparison group.

As a result, the FDA asked that we conduct a literature review to provide insight into the efficacy and safety of conventional chemotherapy in patients with AML in

first relapse, and asked that we include this literature review in our New Drug Application.

We performed a comprehensive review of the literature on the treatment of patients with AML in first relapse. In addition, we conducted an extensive search for institutional databases that might contain relevant data.

For the literature review we conducted a MEDLINE search for articles on relapsed or refractory AML published after 1979. From over 500 abstracts we then selected more than 100 publications for more detailed review, and we searched the bibliographies of these articles to make sure that no other articles had been missed.

The articles selected by the literature review were those that had enrolled at least 20 adult patients with untreated AML in first relapse and also reported information on age and duration of first remission. The studies selected utilized available single agent and combination regimens.

[Slide.]

Most of the 22 studies selected by the literature review utilized combination chemotherapy regimens. Twelve studies were prospective and 10 studies were retrospective, and the 22 studies included 1,890 patients.

There were a number of variations, but many regimens included cytarabine and anthracycline, which

generally requires inpatient therapy for approximately one week. There were only two studies with single-agent therapy.

[Slide.]

Three conclusions have emerged from an evaluation of these articles. First, remission rates reported in the literature are quite variable. Second, much of the variability can be explained by evaluating the age and duration of first remission of patients in the various studies. It should be noted that older patients are poorly represented in the literature.

For instance, there were no studies that met the criteria for our literature review, that had a median age of patients over 56 years old, compared with the median age of approximately 62 to 65 years old for all patients with AML.

The third conclusion from our literature review was that overall survival was quite limited, regardless of remission rate.

We will now present comparisons of specific efficacy measurements with data from the literature, and then utilize two large institutional databases for comparison with the gemtuzumab Phase II data.

[Slide.]

In terms of survival, patients treated with gemtuzumab had results similar to those of patients on other

regimens reported in the literature.

The median overall survival of patients with AML in first relapse, in the six prospective studies from the literature with this information, varied from 3 to 12 months, compared with a median overall survival of 5.9 months for the 142 patients in the gemtuzumab Phase II studies.

The median survival of remission patients was 3 to 24 months in the two prospective studies from the literature with this information and was greater than 12.6 months for patients in the Phase II studies.

Although no prospective studies in the literature reported these data, the median survival of non-responder patients in the four retrospective studies in the literature was 1 to 2.5 months compared with 2.9 months in the Phase II gemtuzumab studies.

Relapse-free survival was 6.8 months in the Phase II studies, compared with 3 to 25 months reported in the literature. The study that reported a 25-month relapse-free survival rate was an outlier and, otherwise, the 6.8 month relapse-free survival with gemtuzumab would be compared with the other studies that reported 3 to 14 months.

[Slide.]

We were also able to compare our results to those from a large database at the Medical Research Council. Dr.

Appelbaum mentioned an MRC clinical trial in relapsed patients that included 175 patients that were a subset of this much larger database.

The MRC database, kindly made available to us by Dr. Alan Burnett of the University of Wales College of Medicine, consists of data from three recent large trials with more than 5,000 patients with de novo AML.

Data are available for 1,696 patients who attained remission and then had a first relapse. As noted by Dr. Appelbaum, many patients in relapse, and particularly the older patients, do not receive remission-inducing treatment.

In this case, 22 percent of the patients received palliative therapy or no therapy on relapse. Overall, 1,221 patients did receive remission-inducing therapy with various combination chemotherapy regimens.

[Slide.]

Overall survival is almost identical in the MRC database and in the Phase II studies with gemtuzumab. In the MRC database, of the 1,221 patients who received conventional combination therapy, the median age was only 46, and the median duration of first remission was 9.8 months.

The MRC definition of remission required only the absence of blasts in a bone marrow exhibiting trilineage recovery. The MRC study had a second remission rate of 49

percent. The two main differences between the MRC study and the gemtuzumab ozogamicin studies, the difference in median age of the patients and the difference in definition of remission, may have influenced the reported remission rates.

Most importantly, the overall one year survival rate for the patients receiving remission-inducing therapy in the MRC database is 32 percent, which is very similar to the 31 percent overall one year survival for patients in the gemtuzumab studies.

Therefore, even though there are differences in age and duration of first remission that limit comparisons of remission data, these data confirm that the overall survival seen in the gemtuzumab Phase II studies is consistent with that observed in the largest institutional database available.

[Slide.]

Data from the M.D. Anderson Cancer Center, kindly provided by Dr. Eli Estey, demonstrate that the overall survival of patients in both younger and older age groups was comparable to that of patients treated with gemtuzumab.

These data are from patients with AML in first relapse treated with high-dose cytarabine-containing regimens at M.D. Anderson Cancer Center over the last 20 years.

The probability of survival at one year for

patients less than 60 and 60 years and older are comparable to that of patients treated with gemtuzumab in the Phase II trials.

Although these data do not take into account differences in duration of first remission, they indicate that both younger and older patients treated with gemtuzumab have overall survival rates comparable to that of large groups of patients treated aggressively at a major cancer center.

[Slide.]

As Dr. Sickels indicated in his introductory remarks, the original NDA contained data on 104 patients. A three-month update included 38 additional patients, for a total of 142 patients in the Phase II studies. We have presented data on 142 patients in the three-month update in our presentation.

Please note that the FDA presentation, which you will hear shortly, refers in part to the NDA group of 104 patients. As indicated on this slide, both patient groups have similar efficacy as measured by remission rate, overall survival, and probability of survival beyond one year. We have also included data on relapse-free survival in the three-month update group.

[Slide.]

In summary, the efficacy data demonstrate that the

remission rate following gemtuzumab monotherapy for the 142 patients in the Phase II studies was 30 percent. Importantly, gemtuzumab was effective both in younger and in older patients. The median relapse-free survival for all patients was 6.8 months and the overall one-year survival was 31 percent.

Our review of the literature and of two large institutional databases confirms that the overall survival and duration of remission seen in the Phase II gemtuzumab studies is comparable to that seen after conventional therapy of patients with AML in first relapse.

[Slide.]

We will now move to the adverse event profile of gemtuzumab. The safety presentation will focus on the Phase II studies, in which all 142 patients received 9 mg/m^2.

We will first present an overview of the safety profile and then provide more detailed information on clinically relevant adverse events. We will also report on the duration of hospitalization and on deaths during the treatment period.

[Slide.]

Most of the adverse events reported in the Phase II studies were not serious adverse events and were mostly of NCI Toxicity Grade 1 or 2. This table lists all non-hematologic treatment emergent events with an incidence of

greater than 30 percent for Grades 1 to 4.

Treatment-emergent events were those that occurred after gemtuzumab therapy started, regardless of relationship to gemtuzumab administration. This definition has been used because of the difficulty relating adverse events to specific causes in critically ill patients, such as these. Hematologic adverse events will be considered separately.

The adverse events listed here, such as fever, chills, nausea, vomiting, and asthenia, are common events in patients with AML regardless of treatment. Events of Toxicity Grade 3 to 4 are of greater clinical concern than Grade 1 or 2 events in acutely ill patients with relapsed AML, and therefore only events of Grades 3 and 4 will be presented from this point in the presentation.

Notably lacking here is alopecia, as there has been no alopecia reported after gemtuzumab therapy. Gemtuzumab therapy was also not associated with drug-related severe CHF, as can occur with anthracyclines, or with severe CNS toxicity, as can occur with cytarabine.

[Slide.]

Just as in the Phase I study, intravenous administration of gemtuzumab was associated with transient infusion-related adverse events in the Phase II studies. Infusion-related adverse events were defined as all those reported the same day as gemtuzumab infusion.

Transient fever and chills were the most common. Hypotension also occurred, leading to I.V. fluid administration in 4 percent of patients. All of these adverse events were transient, and were generally less severe following dose 2 than after dose 1.

[Slide.]

Gemtuzumab targets CD33-expressing cells, and hematopoietic progenitor cells are known to express CD33. Therefore the occurrence of myelosuppression was not unexpected. More than 90 percent of patients had severe neutropenia and thrombocytopenia.

The time to neutrophil recovery to an ANC of 500 was somewhat longer than in other studies. This graph shows the time to recovery of ANC to 500 neutrophils for the 42 overall remission patients, all of whom later reached an ANC of 1,500.

The median time to an ANC of 500 was 40.5 days from the first dose of gemtuzumab. The median time to an ANC of 500 in the literature on treatment of AML in first relapse was 17 to 41 days. Recovery of neutrophils may have been prolonged because of the relatively late administration of the second dose of gemtuzumab on approximately study day 15, compared with other regimens, which end the administration of therapy earlier.

Our data suggest that there was moderate

prolongation of platelet recovery in gemtuzumab-treated patients, consistent with the expression of CD33 on hematopoietic progenitor cells involved in platelet recovery.

Although data on platelet recovery were sometimes limited by the administration of post-remission therapy or salvage therapy, it is clear that CRp patients had slower platelet recovery than did CR patients.

In this figure we have displayed the time to recovery of platelet count to 25,000 for the CR and CRp patients. These patients were all platelet transfusion-independent, that is, patients who had not received a platelet transfusion for at least a week before any of these blood counts.

Eighteen of the 19 CRp patients recovered to a maximum platelet count of greater than 25,000. The median time to a platelet count of 25,000 was 34 days from the first dose of gemtuzumab for the CR patients, and 51 days for CRp patients.

Although not shown on this slide, moderate prolongation of platelet recovery was also seen in the CR patients. The median time to a platelet count of 100,000 was 50 days from the first dose of gemtuzumab for CR patients in the gemtuzumab Phase II studies, compared with 28 to 47 days in the literature on treatment of AML in first

relapse.

CRp patients did require more red blood cell transfusions and more platelet transfusions during the treatment period than did CR patients. Nevertheless, the occurrence of severe bleeding was similar in CR and CRp patients, with one episode of epistaxis in a CR patient and one episode of hematuria in a CRp patient.

[Slide.]

Gemtuzumab therapy was associated with a very low rate of severe mucositis. Mucositis affects the entire GI tract, and the occurrence of severe mucositis during neutropenia predisposes patients with AML to infectious complications by breaking down mucosal barriers that help to prevent infection.

In the Phase II studies only 4 percent of patients had severe mucositis. Included in these was one patient who developed severe mucositis after other chemotherapy was administered.

The rate of severe mucositis reported in studies in the literature on AML in first relapse had a range of 3 to 34 percent. While the literature documents a range of mucositis rates, it should be noted that the studies with at least 50 patients had rates of severe mucositis that were 5, 9, 18, 23, and 33 percent. Therefore, the results seen here are low compared to the results of other therapies.

[Slide.]

The decreased incidence of mucositis led to a low rate of severe infections. Twenty-eight percent of patients had severe, that is, NCI Grade 3 or 4, infections. Despite the low rate of mucositis, the most common severe infections were sepsis and pneumonia.

Nevertheless, the rate of 28 percent of patients with severe infections compares favorably with the range of 29 to 65 percent reported in the literature on the treatment of AML in first relapse. We interpret these results as indicating that the lack of severe mucositis during the neutropenic period reduced the incidence of severe infections.

[Slide.]

Gemtuzumab administration was associated with a moderate incidence of elevated hepatic transaminase and bilirubin levels. Abnormal liver function tests were predominantly to Grade 3. There were 17 percent of patients with Grade 3 or 4 elevations of hepatic transaminases and 23 percent of patients with Grade 3 or 4 elevations of bilirubin.

These low rates of transaminase and bilirubin elevations were moderately higher than studies in the literature. Elevations of hepatic transaminases and bilirubin were transient and only rarely associated with

other evidence of liver dysfunction.

[Slide.]

In the Phase II studies, there was no evidence of an immune response against the protein or calicheamicin component of gemtuzumab. Both Phase I and II clinical trials included laboratory evaluations to detect an immune response against the antibody component, as well as against the calicheamicin-linker component of gemtuzumab. No antibodies to the antibody component were detected.

In the Phase I clinical trial, two patients had immune responses against the calicheamicin-linker component of gemtuzumab. One patient had no related symptoms. The other patient had mild shortness of breath for 10 minutes associated with decreased drug concentrations. That patient has a remission at a lower dose of gemtuzumab and, approximately six months later, had relapsed and received a second course of gemtuzumab when this reaction occurred.

In the Phase II studies, there were no immune responses detected against either component of gemtuzumab. Therefore, there appears to be no clinical evidence of immune response to gemtuzumab when administered as a two-dose regimen to patients with AML in relapse.

[Slide.]

Compared to patients reported in the literature, patients in the Phase II studies spent fewer days in the

hospital during the treatment period. Almost 20 percent were hospitalized for seven days or less during the treatment period.

Strikingly, 4 percent of patients required no hospitalization and, including this 4 percent of patients, there were 19 percent of patients with 0 to 7 days of hospitalization. The median duration of hospitalization for all 142 patients was only 24 days.

To place these data in perspective, it must be recognized that hospitalization is considered routine in the treatment of patients with relapsed AML. The literature does not report patients who have not been hospitalized during their course of AML treatment. Only one reported study in patients with AML in first relapse included data on the duration of hospitalization, which was a mean of 38 days.

Therefore, we expanded our review of the literature on hospitalization to include patients with initial presentation of AML. In that population, which is generally expected to have fewer complications than patients with relapsed AML, the median duration of hospital ranged from 22 to 43 days. Taken together, these data suggest that treatment of patients with relapsed AML is associated with a decreased duration of hospitalization compared to conventional therapies.

[Slide.]

Gemtuzumab therapy is associated with a lower mortality rate in older patients compared to other therapies. For the gemtuzumab Phase II trials, the mortality rate of 15 percent shown here included deaths from any cause occurring from the first dose of gemtuzumab to day 50 of the study, which is consistent with the range of 3 percent to 32 percent reported in the literature on AML in first relapse.

Dr. Estey from the M.D. Anderson Cancer Center has provided data on the mortality rate in 126 patients, 60 years of age and older, with AML in first relapse treated with high-dose cytarabine regimens at his institution over the past 20 years.

While these data are in patients with varying durations of first remission and other characteristics, they indicate that although these patients had remission rates similar to patients treated in the gemtuzumab studies, they had a much higher mortality rate of 29 percent.

These data document a lower mortality rate in patients treated with gemtuzumab compared to other therapies.

[Slide.]

The safety profile of gemtuzumab was the same in the 142, three-month update patients, as it was in the 104

original NDA patients. The data shown here indicate that both patient groups have a similar safety profile as measured by rates of severe mucositis and infection, and by the duration of hospitalization and early mortality rate.

[Slide.]

In summary, the safety data demonstrate that targeted therapy for AML with gemtuzumab as a single agent was associated with a favorable overall adverse event profile. Specifically, there was a decreased rate of several types of serious side effects compared to combination therapies. These was a very low rate of severe mucositis associated with a low rate of severe infection.

The outpatient nature of gemtuzumab administration, as well as the low rate of severe infections, led to reduced hospital stays for these patients, and in older patients who participated in our studies, there was a lower rate of death during the treatment period compared to other therapies.

The data we have presented on the effects of gemtuzumab ozogamicin, the first antibody-targeted chemotherapy agent, clearly demonstrate that targeted therapy for patients with relapsed AML is both safe and effective.

Thank you.

Dr. Matthew Sherman will now review the

benefit/risk profile of gemtuzumab ozogamicin.

Benefit/Risk Assessment and Conclusions

DR. SHERMAN: Thank you, Mark.

[Slide.]

Members of the committee, good morning. I am Dr. Matt Sherman, Head of Oncology Clinical Development at Wyeth-Ayerst Research, and it is truly a pleasure to be here today.

[Slide.]

AML is a serious and rapidly progressive and fatal disease. If untreated, the median survival is less than three months.

As we have heard from Dr. Appelbaum, while the remission rates in patients with de novo AML can be high, unfortunately, the majority of these patients relapse.

These relapsed patients have a particularly poor prognosis with less than 5 to 10 percent of these patients living beyond five years.

Because current therapies are associated with severe toxicities, up to 25 percent of patients with relapsed AML do not receive treatment. Despite decades of research, no single agent or regimen has emerged as the standard of care for patients with relapsed AML.

[Slide.]

Gemtuzumab is the first antibody-targeted

chemotherapy. Based on data presented today, we have determined that gemtuzumab has a well-defined safety and efficacy profile and thus a favorable benefit/risk relationship.

When treated with gemtuzumab as a single agent, patients can be induced into remission.

The ease of a two-dose and two-hour I.V. infusion schedule and manageable infusion related side effects allows gemtuzumab to be administered in the outpatient setting.

Lastly, compared to conventional therapies for AML, patients treated with gemtuzumab have both reduced toxicity and a reduced need for hospitalization.

[Slide.]

We have observed consistent efficacy with gemtuzumab as a single agent in three open-label studies.

Moreover, the 142 patients who participated in these studies were representative of patients with relapsed AML.

The results of these studies clearly demonstrate that as a single agent, gemtuzumab has an important role in the treatment of patients with AML, both in younger patients enabling them to proceed into bone marrow transplantation and in older patients who are most affected by this disease and who are unable to tolerate conventional chemotherapy.

[Slide.]

The incidence of AML increases progresses with age, and as a result, more than half of the patients are greater than age 60.

Published studies show that older patients have lower response rates and higher death rates compared to younger patients.

As we have heard earlier, in our studies, the median age was 61 years and the duration of first remission, 11.1 months.

Despite these unfavorable prognostic factors, patients responded well to gemtuzumab, indicating that it is an effective and safe therapy regardless of age or duration of first remission.

[Slide.]

Based on a comprehensive review of the literature and analysis of two large institutional databases, we found that the effectiveness of gemtuzumab was comparable to that of conventional chemotherapy.

When we analyzed for the two most important prognostic factors of age and duration of first remission, we found that remission rate, relapse-free survival, overall survival, and survival following transplantation in the gemtuzumab studies were comparable to the rates reported in the literature.

[Slide.]

Gemtuzumab demonstrated a favorable safety profile that benefitted patients. This included a very low rate of infectious complications and a low rate of severe mucositis. Additionally, patients treated with gemtuzumab had fewer days of hospitalization. Remarkably, 19 percent of patients had less than eight days and 4 percent of patients did not require any days of hospitalization, representing a new milestone in the treatment of AML.

Furthermore, no alopecia or drug-related cardiotoxicity or cerebellar toxicity was seen as might be expected for other agents.

However, elevations of liver function tests did occur and hepatic veno-occlusive disease was seen in a minority of patients, but should not limit the ability to administer gemtuzumab to the majority of patients.

The majority of adverse events that we did observe were mild to moderate, reversible, and related to an acute infusional syndrome.

While patients commonly reported fever, chills, nausea, and vomiting, the incidence of severe bleeding was similar to other regimens used to treat these patients.

[Slide.]

We found that patients treated with gemtuzumab can achieve either a complete remission or a complete remission with delayed platelet recovery.

Both groups benefitted from gemtuzumab with clearance of leukemic blasts, recovery of neutrophils, and platelet transfusion independence.

We believe that the delayed platelet recovery is in part a result of gemtuzumab's ability to target CD33 on the megakaryocyte progenitor cells.

The data show that CRp patients require more platelet and RBC transfusions, but more importantly, the overall safety profile of CR and CRp patients was similar.

In contrast to this minor difference in transfusion requirements, the efficacy outcomes of CRp patients based on both relapse-free survival and survival following transplantation were comparable to the CR patients.

Again, this suggests that patients will benefit from gemtuzumab whether they achieve a CR or a CRp.

[Slide.]

In conclusion, there is a critical need for improved therapies for the treatment of relapsed AML.

Gemtuzumab ozogamicin is a novel anti-CD33 antibody that targets myeloid leukemic cells without damaging non-hematopoietic tissues.

We believe the data presented this morning support the proposed licensure of gemtuzumab for the treatment of CD33-positive relapsed AML.

These data clearly demonstrate that patients treated with gemtuzumab as a single agent achieve a remission with reduced toxicity and a reduced need for hospitalization.

Gemtuzumab can be administered safely in the outpatient setting. Side effects are generally manageable, low grade, and generally reversible.

Gemtuzumab is novel, safe, and effective. If approved, gemtuzumab will fulfill an unmet medical need and become an important treatment option for patients with relapsed AML.

Thank you very much.

DR. SCHILSKY: Thank you, Dr. Sherman.

We have time now for some questions from the committee.

Dr. Nerenstone.

Questions from the Committee

DR. NERENSTONE: You did not include any secondary AML or patients who had pre-existing myelodysplastic syndrome in your clinical trials.

Is that because you expect them to somehow--I know clinically, they don't usually do as well in terms of secondary treatment, but do you expect those patients to somehow respond differently or just in lower numbers, or do you have any other information about their treatment?

DR. SHERMAN: The question relates to the inclusion of criteria for these studies, and particularly the exclusion of patients with secondary AML or myelodysplastic syndromes or an antecedent hematologic disorder.

The design of these trials were particularly challenging, and we received the input from many investigators, and it was of the belief that because of the extreme heterogeneity of the patients with relapsed AML, and particularly the very poor prognostic factors with secondary AML and an antecedent myelodysplastic syndrome, those were felt to be important reasons to exclude those patients from the clinical trials.

We don't have any data one way or the other to suggest that those patients would particularly respond or not respond to gemtuzumab.

DR. SCHILSKY: Dr. Blayney.

DR. BLAYNEY: What other cells in the body have CD33 antigens on them?

DR. SHERMAN: The data available shows that CD33 is restricted only to the myeloid compartment of cells, so to the earlier CFU stem cells, as well as to the myeloid cells.

DR. BLAYNEY: You mentioned or you showed in your slide that you had pretreatment cytogenetic analyses on

approximately 100 of your 142 patients. What information do you have on the cytogenetics post-gemtuzumab therapy?

DR. SHERMAN: This question relates to the cytogenetics of patients enrolled into the study, and we did obtain cytogenetic markers when available for patients who were enrolled in the study, both at baseline and at the time of their relapse.

As was shown earlier by Dr. Berger, only 5 percent of the patients overall fell into the favorable category of cytogenetics, so the majority of patients who were treated did have either intermediate or poor prognostic risk factors for cytogenetics. We did not specifically measure cytogenetics at the time of remission, so we have no data at the time.

DR. BLAYNEY: You have no data on cytogenetics post-gemtuzumab treatment?

DR. SHERMAN: No, that was not a routine test that was obtained.

DR. BLAYNEY: It would give me some comfort in knowing that as a marker of remission, if you have that data.

DR. SHERMAN: I think it was obtained at individual investigator sites. I am not sure if Dr. Appelbaum would want to report any information that was available for patients that he treated.

DR. APPELBAUM: We, as Matt said, we don't have routine cytogenetics on all of the patients that were entered on study. On those cases that we studied in Seattle, where there was a complete remission obtained, all of them were cytogenetically normal.

We did not see any patient who obtained a remission that had clonal disease as measured by cytogenetics. That was done by routine cytogenetics, we did not do in those few cases where you have PCR-based assays for the particular translocation, we did not do detailed PCR bases.

I would point out that in the cooperative group studies, that is not routine either, because we actually don't know how to interpret the results of PCR-based studies yet.

DR. SHERMAN: Maybe we can also show some information on the slide B-31, please.

[Slide.]

These are the data that show remission rates by the cytogenetic risk category. As you can see, very few of the patients had favorable cytogenetics where the majority of the patients had intermediate or poor risk cytogenetics, and yet these patients clearly comprised the responding group of patients, as well.

DR. BLAYNEY: Thank you. That is very helpful.

In the recurrent patients or who recur after gemtuzumab treatment, do they also evidence CD33-positive? Do they show CD33 on their cells, the blast cells?

DR. SHERMAN: This question relates to patients who relapse after gemtuzumab, and whether or not they show CD33. Let me answer this question actually in two different ways. Yes, in patients who relapse following gemtuzumab, some of those patients do re-express CD33, and in the course of these studies, we allowed subsequent courses of gemtuzumab for patients who did initially have a response and then relapsed.

In the 142 patients who were discussed today, 4 patients received more than one course of gemtuzumab. One of these patients has gone on to multiple remissions, and just for illustrative purposes I would like to show the figure for that patient. Slide B-29, please.

[Slide.]

This is a 75-year-old male who was treated with gemtuzumab ozogamicin. He received his first treatment in December of 1997. He was by eligibility criteria, of course, CD33-positive.

He achieved a complete remission. This complete remission lasted for six months. This patient subsequently relapsed. Again, to be eligible for retreatment, he had to fulfill all the criteria for eligibility with the initial

protocol including CD33 positivity.

He received a second course of gemtuzumab, had a second complete remission with clearance of his leukemia blasts, full recovery of hematopoiesis. His second remission after gemtuzumab lasted for nine months.

He recently relapsed for a third time, again was CD33-positive, again was treated, had a full remission, recovery of his blood counts, and he remains in a complete remission at this time. So, he has been treated for more than two years since his first exposure to gemtuzumab.

DR. BLAYNEY: I suspect that is maybe how this compound is going to be used in many cases.

The last thing, you have evidence on stability of the linker DNA moiety, how stable those are when this compound is prepared and shipped to the site where it is going to be used, that remained stable for a long time?

DR. SHERMAN: This question relates to the stability of the linker. The linker is a covalent bond, it is fully stable, and does not release calicheamicin until it is activated intracellularly.

DR. BLAYNEY: Thank you.

DR. SCHILSKY: Dr. Berman.

DR. BERMAN: Do you have any data on how many patients were CD33-positive at their local institution, but, in fact, were not broad enough to be eligible for the trial

when the reference lab looked at the CD33?

DR. SHERMAN: This question relates to the expression of CD33 both at the local sites, as well as at the central laboratory, and as we presented, we did have criteria for eligibility for CD33 positivity that was confirmed at two central laboratories.

Local laboratory positivity was not required for entry into the study, so we don't have data for all patients.

If I may see Slide B-14, please.

[Slide.]

This shows in a limited number of patients when we asked certain sites to submit the local flow data, as well as the central flow data, this shows the concordance between the central flow laboratory, as well as the local flow. In the majority of cases, there were patients that were both locally positive, as well as positive at the central flow laboratory.

DR. SCHILSKY: Dr. Albain.

DR. ALBAIN: Thank you. Could you compare your data to any data that might exist on anti-CD33 antibody alone, and is there any data on the antibiotic component alone yet, the calicheamicin alone?

DR. SHERMAN: The question is whether we have data with the naked antibody alone and whether or not there is

information about calicheamicin as a single agent.

We have not performed any studies with the humanized antibody as a naked antibody, unconjugated to calicheamicin. There is information that has been published, and this is with the murine form of the antibody that was radio labeled for distribution studies.

Actually, I would like to ask Dr. Appelbaum to come forward to report on some of those studies with the murine antibody.

DR. APPELBAUM: Very briefly, using this CD33 antibody in murine form with trace amounts of I-131 on it, in part of a study where we began trying to target radiotherapy to the marrow for purposes of augmenting the radiation we were using in a transplant approach, we found that the antibody alone again had some infusional side effects with fever, mild fever in some patients. Otherwise, it was well tolerated. We did see transient decreases in the number of circulating leukemic blasts, but we never saw a remission or major reduction in the amounts of leukemia in the bone marrow.

The group from Sloan-Kettering has done extensive studies using the humanized anti-CD33 antibody, not the same one, but their M-195, and that group has extensively studied this approach.

In their hands, their M-195 also leads to

reduction in circulating blasts, but generally does not lead to complete remissions in patients with overt leukemia. I believe they have had one CR in about 50 or so cases.

They are continuing to study the unmodified M-195 in an adjuvant setting, so that patients who are in complete remission, but have evidence of minimal residual disease as manifest by PCR positivity, for instance, in APL, are being treated, and what they find is that the unmodified antibody in that circumstance can change some patients from being PCR-positive to being PCR-negative, but that is in the setting where they have minimal disease, not where they have overt leukemia.

I think most people that have studied CD33 agree that the unmodified antibody is incapable of inducing substantial remissions in patients.

DR. ALBAIN: And the calicheamicin alone?

DR. SHERMAN: The second part of the question was about calicheamicin alone, and we have not, and to my knowledge, no one has administered calicheamicin as an antitumor agent.

DR. SCHILSKY: Dr. Santana.

DR. SANTANA: I have two questions that are kind of linked. In real practice, we still use FAB classification, so I was struck on your report on page 22, Table 10, that at the time of relapse, a large number of

your patients had FAB undetermined.

Have you looked at your response rates based on FAB on your data?

A corollary to that is have you looked at the bone marrow cellularity components of your patients that you are calling on CRp versus those that are true CR's?

DR. SHERMAN: There are two parts. The first question relates to the FAB classification of leukemia and whether or not we have looked at the response rates according to FAB classification.

We do actually have data that we have presented in the background packet about FAB classification. We have not looked at the response rates according to the various FAB classifications. We do note that we have only one patient with M3 classification. Otherwise, most of the patients were represented either by M1 or by M2 classification.

DR. SANTANA: And the follow-up in terms of the issue of the cellularity of making this distinction between CR and CRp's, how did the cellularity of the bone marrow biopsies compare between those two groups?

If you are implying that the CRp's is because there is some toxicity to megakaryocytes, and those patients are true remissions, it is just that the therapy somehow kills megakaryocyte precursors, but were there issues of cellularities between those two groups in the biopsies?

DR. SHERMAN: As far as we could tell, there was no difference histopathologically in the bone marrows of the patients with either CR or CRp in terms of cellularity or in megakaryocyte numbers.

DR. SCHILSKY: Dr. Lippman.

DR. LIPPMAN: This follows up in part on Dr. Blayney's question, and it relates to the fact that there are 142 patients and 53 centers.

Do you have a breakdown of the number of patients at each center, because I had a couple of questions regarding this, but one is Dr. Appelbaum said that all of his CR patients went into cytogenetic remission. How many patients was that?

DR. SHERMAN: Could you repeat the last part of that question? The first part of it was related to the number of patients per center.

DR. LIPPMAN: Per center, if you have a breakdown there, because it looks like each center had two to three patients, unless there was some difference in that, and then relating to the cytogenetic question, I wanted to follow up on the patients Dr. Appelbaum treated, how many patients were we talking about that went into cytogenetic complete remission.

DR. SHERMAN: First, let me address the question about the number of centers. Again, these were global

studies, and they were done obviously both in the U.S. and in Europe, and there were a number of centers in both continents.

We have looked at--the most relevant answer would be to the patients in the 201 study, which were 65 patients that was conducted in the United States and in Canada, and we have looked at the remission rates at the various centers who were the most highly enrolling centers. If we can show the slide with remission rates by center.

[Slide.]

This shows all the centers involved in the 201 study, so 65 patients were enrolled overall, and the corresponding response rates for those different centers. If you look at the four highest enrolling centers, with 10 of more patients, you can see that while there is some variation in the number of patients responding, there were responses seen in all these centers.

DR. LIPPMAN: If you can leave that slide up, because, again, the lack of a control study, and looking at these ranges, it is hard to interpret. You make a big point of comparing M.D. Anderson experience.

I guess in this study, it was 18 percent, but when you are comparing those numbers of the HIDAC regimens, are those patients treated on protocol, are those selected patients treated on protocol, or are these patients

primarily treated off protocol with perhaps many different adverse prognostic factors?

DR. SHERMAN: I would like to ask Dr. Berger to come up and to address the questions about the comparison of our data with the literature group.

DR. BERGER: I believe your question related to the treatments received by the patients at M.D. Anderson who we noted in our comparison. Those were all patients treated over the last 20 years with various others, the cytarabine-containing regimens, so they weren't on one particular study.

Those patients were entered into multiple studies receiving high-dose cytarabine, and some of them were not on particular studies, but they are the entire experience of that institution with high-dose cytarabine-containing regimens.

DR. LIPPMAN: My concern relates to the fact that you are comparing a fairly current, fairly well-described eligibility criteria protocol and focusing on age and important differences using that experience, and I just am not sure how comparable those comments are to a 20-year experience with many other potential adverse prognostic factors.

DR. BERGER: Right. As we explained, we did our best to find the largest institutional databases we could

find because there weren't large studies published in the literature review that we did, and that is the second largest institutional database we were able to find, so that data obviously represents data over several years, but obviously represents data over a period of time when patients were not initially treated with high-dose ara-C-containing regimens before relapse either.

DR. LIPPMAN: My last question relates to the endpoints. Was the CR defined by platelet criteria a primary endpoint of this study?

DR. BERGER: Yes, CR is defined by the criteria you mentioned, was the primary endpoint.

DR. LIPPMAN: So, CRp's was a primary endpoint?

DR. BERGER: No, CRp was a secondary endpoint of the study as originally written.

DR. LIPPMAN: Is that an accepted endpoint in the literature? Are there other studies and protocols that are using that endpoint?

DR. BERGER: We have actually looked at the CRp rate in the literature, and perhaps we could take a look at that. Basically, the conclusion is that CRp rate in other studies in first relapse in the literature is very low. It's 5 percent or less. We have done that with actually--I would like to see Slide B-20 to show this data in two different ways.

[Slide.]

The first was that a definition relevant to CRp wasn't directly measured in any study in the literature review. There is one study that reported a partial remission rate of less than 5 percent and included both incomplete blast clearance and patients with incomplete recovery of platelets, not the same thing, but I would point out that our CRp rate does not include any patients with partial remission at all, but nevertheless, the rate in that study was 5 percent or less.

In addition, we have also looked at two other databases. Dr. Estey look at 200 patients in his database and found that 5 percent of patients would satisfy a definition for CRp, but not a definition for CR, so in his database, the number of patients with CRp was 5 percent.

In addition, we looked at a somewhat smaller database at the University of Vienna, and found that of their patients, 3 percent would satisfy the definition of CRp, but not CR.

Both of these databases were looking at patients in first relapse, therefore, comparable in terms of relapse status to our patients, and our conclusion from this is that the CRp rate in studies in the literature with other regimens is 5 percent or less, and therefore wouldn't add appreciably to the CR rates that are already published.

DR. SCHILSKY: Dr. Sledge is next.

DR. SLEDGE: A couple of questions. If I am reading one of your slides correctly, 66 patients got no further therapy after gemtuzumab, and of these, 23 were either a CR or CRp.

Now, realizing the selection biases that must have put you into that group, how did the responders in that group do in terms of median duration of response, and were there long-term survivors after getting gemtuzumab alone?

DR. SHERMAN: If Dr. Berger will come back to the podium to also answer this question, which relates to the additional chemotherapy that was given to patients following gemtuzumab, and in some patients they could receive no further therapy, a bone marrow transplant, or additional chemotherapy.

DR. SLEDGE: Right. If I am reading it correctly, 23 patients had either a CR or a CRp in your no further therapy group. So, how did they do in the long run?

DR. BERGER: In our group of patients who had remission, of the 42 remission patients, you are correct that there were 23 patients who had no further treatment.

If I could show Slide B-2.

[Slide.]

What we can show is that for those patients who had--this is the no further therapy group of 23 patients--

the median duration of remission in those patients was 2.1 months, and the total median survival of those patients was 12.8 months.

Remember that patients who had no further therapy consisted largely of patients who were 60 years of age and older, and thus weren't eligible for, for instance, transplant.

The 15 patients who had hematopoietic stem cell transplant, 14 of them were less than 60 years old, as you might well expect, and were able to get transplant. There were also 4 other patients who were able to get other additional anti-leukemic therapy.

DR. SLEDGE: Do any of those no further therapy patients have durable remissions or was it a common experience that they virtually all fell out of remission in a few months?

DR. BERGER: No, we can show specific data on the groups of patients within this in just a second, but the answer is that there are several patients who have long-term remission at this point, but remember that the median duration of patients in first relapse who do not get another treatment, in most literature studies, is approximately 6 months. So, one should expect that if you don't give other treatments.

I believe we actually have some information here

in B-46.

[Slide.]

That will show the total survival with gemtuzumab only, and this is the Kaplan-Meier curve showing that there are a couple patients still continuing, and this gives you a better sense of the time from first dose and how patients have actually done. But as I said, I think the important thing to remember is that we are unlikely to be a magic drug that is different from the literature with other treatments with a mean duration of approximately 6 months.

DR. SLEDGE: A second question. If we look at other monoclonal antibodies that have been used for anti-cancer therapy, frequently what has been seen in terms of responses is the relationship between the number of antigen targets on the cell and the overall response rate.

You, in presenting this data, basically have talked about positive and negative for CD33, but I would assume that among your CD33 positives, there is a range of positivity.

Do you have any data or any sense in terms of whether or not people who are strongly CD33-positive do better than those who are more weakly positive, but still meet your entry criteria?

DR. BERGER: Yes. We built into the study a measurement of quantitative CD33 expression, which is

basically a measurement of the expression level over the baseline level for each patient.

We have done a multivariate analysis, an exploratory multivariate analysis of our data, which shows that the level of CD33 expression did not relate either to the likelihood of remission or to the likelihood of survival in these studies.

Obviously, we built the quantitative measurement into the study because we thought there might be such a relationship, and we don't see it. If you look in a univariate manner, there is such a relationship, but not in a multivariate study, a multivariate analysis.

DR. SCHILSKY: Dr. Berman.

DR. BERMAN: You described about a 3 percent case, a 3 percent incidence of tumor lysis syndrome, and in one of those patients, he or she had gotten a rapid infusion, less than the recommended two hours of the antibody.

Is there a rate-related toxicity if the antibody goes in over less than the recommended two hours?

DR. BERGER: Our answer would have to be anecdotal. That one patient did appear to have a tumor lysis syndrome, and did have a short, I believe approximately 40-minute infusion of gemtuzumab instead of the two-hour recommended infusion.

We just don't have experience with other people

getting rapid infusions or enough patients getting rapid infusions to know whether that is the case or not.

DR. SCHILSKY: Mr. Flatau.

MR. FLATAU: A follow-up, I guess, to Dr. Sledge's question. I think there were 13 patients who were in the OR group, who are long-time survivors, and how many of those had transplants, and how many had just gemtuzumab, and how many had additional chemotherapy? And I guess how long, is it a one-year survival?

DR. BERGER: I am sorry, I couldn't hear the last part of the question.

MR. FLATAU: How long were they in remission? I think it was one year or two years?

DR. BERGER: I believe the question relates to the overall remission patients in terms of how long patients were in survival.

MR. FLATAU: The ones that are long-term survivors, you said there were 13 long-term survivors in the OR group.

DR. BERGER: Right. So, the question relates to information on the length of time of the long-term survivors in the OR group. I believe we can show the survival curve again. I think that might answer that question.

MR. FLATAU: I wanted to know how many had transplants and how many had additional chemotherapy, and

how many just had gemtuzumab.

DR. BERGER: Oh, I see, I am sorry. So, the question relates to long-term survivors, how many patients had transplants, how many had no therapy, how many had other therapy.

In general, most of the patients in the study who were long-term survivors did have transplant. There are several patients who have not had further therapy, who are also long-term survivors. I am not sure we will be able to provide numbers immediately. We might have to try to figure that out to be able to display it to you.

But the answer is that most of the patients who are long-term survivors have had transplant, as one would expect with a disease with a median relapse-free survival is about six months in most patients.

If I can show Slide B-83.

[Slide.]

This might relate somewhat indirectly to answer your question. This is overall survival after hematopoietic stem cell transplantation. If one looks at the OR group, which is a combination of the CR and CRp groups, patients who had transplant have a survival of greater than 8 months at this point, and the minimum is less than 1 month, because it's recent, and the maximum is 24 months.

So, I guess to be able to answer your question,

the maximum is 24 months here in terms of patients who have survived after transplant.

DR. SCHILSKY: Dr. Przepiorka.

DR. PRZEPIORKA: Two questions, please, to follow up again on the patients with CR versus CRp.

When you showed us the relapse-free survival for those receiving no further therapy after achieving a CR/CRp, it was down to 2.1 months now. If you were divide that group up into the CR versus the CRp patients, was there a difference in relapse-free survival of those receiving no therapy?

DR. BERGER: Sure. We can show a Kaplan-Meier curve of the survival of those who received no further therapy divided into CR and CRp groups. I will show that in a second. The overall answer to your question is that there is no demonstrable difference between those groups of patients. I would point out they are relative small groups, but nevertheless, we will be able to show that.

If we can show Slide B-45, then, perhaps after that a Kaplan-Meier curve. Better yet, let's show the Kaplan-Meier curve.

[Slide.]

This is data with CR and CRp patients who received no further post-remission therapy, and although there is some difference in the curves, you see a log-rank test, at

this moment it says that in terms of the differences between the curves, they are not significant.

Obviously, we are talking about small numbers here, and so I would urge you to remember that, but nevertheless, this is the data we have at this point.

DR. PRZEPIORKA: My other question is for the patients who did go on to get other therapy after not achieving a remission, how many of them achieved a remission with their second salvage, and how many were unable to get a second salvage because of cumulative toxicities from gemtuzumab?

DR. BERGER: The question relates to the number of non-responder patients who went on to additional therapy, how many of those achieved a complete remission with the second therapy, as well as--I am sorry--the second question is?

DR. PRZEPIORKA: How many could not receive additional therapy because of the hematologic complication?

DR. BERGER: We don't have a solid way to answer the second part of your question. We didn't record how many patients didn't receive additional therapy, but we can provide information on the number of patients who were non-responders, who received additional therapy.

The answer to your question is non-responder patients did very poorly irregardless of whether they got

additional therapy or not. Perhaps I can come back to this if I can.

DR. SCHILSKY: Why don't we go on to another question from Dr. Berman then.

DR. BERMAN: You reported on three or four cases of patients with veno-occlusive disease. Were these following bone marrow transplant or were these following administration of the agent alone?

DR. BERGER: The answer to your question is there are two groups of patients. There were patients who had veno-occlusive disease after receiving allogeneic bone marrow transplant, and we will show that information on Slide B-58.

[Slide.]

In the 142-patient group, after bone marrow transplant, there were 5 patients who had veno-occlusive disease reported. Of these patients, there were 3 patients who expired and 2 patients in whom the VOD resolved.

Of the 3 patients who expired, one of them was a complete remission patient, the other 2 were non-responder patients who nevertheless went on to allotransplant, perhaps in a partial way answering your other question. These patients obviously didn't do particularly well after allotransplant.

Perhaps Dr. Appelbaum can expand on this in a

minute, but this rate of VOD and rate of fatal VOD after bone marrow transplant, and particularly after allogeneic transplant, isn't particularly unexpected at all.

Also, in the 142-patient group, there was one patient reported who developed hepatic failure syndrome with persistent ascites, which at least at one point was called clinical VOD, although a precise diagnosis of VOD was not made by the usual criteria. That patient did die apparently due to hepatic failure after several months.

In addition, in the time period the 142 patients were reported, there was also one compassionate use patient who had an allogeneic transplant and relapsed, and very shortly after that transplant had our drug, and did develop VOD, and actually died of persistent disease, but had developed VOD.

So, that is the experience in the 142-patient group. Perhaps Dr. Appelbaum would like to make a comment on VOD after bone marrow transplant in this particular rate, which is 3 out of 27 patients who received transplant in our experience, which is a 15 percent rate.

DR. APPELBAUM: As you know, Ellin, it really does depend very much on the sorts of regimens that particular institutions are using, but a 15 percent incidence of VOD is within the range of what many people have seen.

We have not experienced in our patients at the

Hutch or in talking to the other investigators, any unusual realm of toxicities after allogeneic transplant for people who are induced with the gemtuzumab either successfully or unsuccessfully.

These are patients with relapsed AML who got aggressive preparative regimens, and we do not believe that this reflects any difference than what might be seen in the literature. We see about--again, it depends on preparative regimen and the relapse remission rate of patients.

DR. BERMAN: Fifteen percent seems a little high for AML second remission, especially in patients who have had a long first remission, so not a lot of chemotherapy in the interim. Can you tell what patients--you probably don't have that, or you may--TBI-containing, more cytoxin, BCNU-containing regimen? It seems high.

DR. APPELBAUM: Well, as I say, if you look overall, at about 10 percent incidence of VOD is what most TBI-containing regimens would reflect, and about a 5 percent fatality rate from VOD in most studies, and it's higher in patients who had prior therapy, it's lower in CML's, it is higher in TBI aggressive regimens than in less aggressive regimens. With the small numbers, I think it is really hard to conclude anything.

I don't have the precise preparative regimens of these patients available to me.

DR. BERGER: If I could return to the previous question with Slide B-44.

[Slide.]

I am not able to answer the question of how many patients had CR in the non-responder group, however, I can show data here that looked at the non-responder group of patients of which there were 100 overall, and their median survival in months, as a group, is 4.2 months.

I think what can be said is that their median survival was not particularly dramatic regardless of what other therapy they got or their response to the therapy.

DR. SCHILSKY: Dr. Simon.

DR. SIMON: It is difficult to evaluate your data, and part of the reason is, you know, there is a certain inconsistency here, understanding what the logic of the basis for the claim is.

You say that you did single arm Phase II trials because there was no standard therapy for AML in first relapse, and then you spend a substantial part of your presentation time making comparisons to the literature in ways that are dissatisfying, I think, for everybody in terms of what we would learn from those comparisons.

A lot of times when people say there is no standard therapy, they mean there is no effective therapy, but here, it sounds like your logic is that there is

effective therapy, and you are comparing your result to other results which you are assuming represent effective therapy in trying to make the case that your therapy, since it's equivalent to the literature, is also effective.

It is really very difficult to sort of see what you have other than a 30 percent response rate with a two-month median maintained duration of responses.

The specific question I had, though, is a follow-up to Dr. Sledge's question. For the 23 patients who had maintained remissions, could you show that slide again, could you just educate me? I thought what I was seeing was a two-month median unmaintained remission rate and a 12-month median survival.

So, what happened? Could you explain that, what happened to the 23 patients who had unmaintained remissions after they relapsed? How did they manage to survive for a median of 12 months?

DR. SHERMAN: The question relates to a Kaplan-Meier analysis of survival data for patients who receive gemtuzumab and then did not go on to further therapy, and as I remember, there was a Slide B-2.

[Slide.]

These are the date of an entire group of responding patients, 42 and of the 23 patients who had received no further therapy, the median duration of

remission was 2.1 months with a total median survival of 12.8 months.

DR. SCHILSKY: I think the question was how do you explain that, how did those patients who have only a two-month median duration of remission manage to survive then for an average of 12 months.

DR. SHERMAN: These patients were eligible to go on to additional therapy, as well, following their relapse after gemtuzumab. So, some of these patients may have received additional therapy.

DR. SCHILSKY: Why are they listed in the No Further Therapy category?

DR. TEMPLE: I think it means no further therapy during the remission.

DR. SHERMAN: I cannot explain the statistic right now. We will have to look at this data and get that answer back to you.

DR. TEMPLE: But isn't what you mean no further therapy during the remission? That is what you mean.

DR. SIMON: I was sort of wondering did they have remissions on a third-line treatment, how many of them did, how many of them went on to further treatment? How many of them did not receive further treatment?

DR. SHERMAN: These patients were categorized as having no further therapy. Then, they relapsed, they would

have had ongoing survival until death, but we would have to go back, and I should look at the Kaplan-Meier estimates to look at these numbers.

DR. SCHILSKY: I have one or two other questions that I would like to ask about. First, I have a question about the dosing and the selection of the dose.

I mean you described very clearly how the dose was selected, although looking at the data that you showed, there doesn't really seem to be any real difference in any of the parameters that led to the dose selection except for the duration of saturation of binding, so that as best as I could tell, at all the doses from 4 mg/m^2 up, the various parameters at the extent of saturation of binding and at the clinical parameters, all of that could be pretty much the same, and 9 was somewhat different in terms of the duration of binding to CD33.

So, I guess my question is while there may be that difference, is that difference actually important? Is there any information from the Phase II trials to suggest that duration of saturation of CD33 is actually an important parameter with respect to any clinical measure?

DR. SHERMAN: This question relates to the dose selection for the Phase II trials, and as Dr. Schilsky has pointed out, there were several parameters that were evaluated in the Phase I trial to choose the dose.

First, it was recognized clearly at the 9 mg/m^2 dose level in the Phase I trial, while acceptable myelosuppression was seen after two doses of gemtuzumab, and patients received a third dose, prolonged myelosuppression was observed. So, at that time it was not felt to be necessary to go up to higher dose levels.

Furthermore, at 9 and even at lower doses, there was complete saturation at the peak, but actually most importantly, the duration of saturation fell off within the first 24 hours at doses less than 9 mg/m^2, and then lastly at 9 mg/m^2 we saw a significant number of patients who had an anti-leukemic response with clearing of bone marrows in the blasts and peripheral blood.

So, on that basis, the 9 mg/m^2 dose was chosen for the Phase II studies and resulted in the data presented with the 30 percent response rate. We have not gone back in these studies to look at other dose levels.

DR. SCHILSKY: I appreciate your summarizing all the data again, but I guess the question is in the Phase I study, there was one patient with a CR at 4 mg/m^2 that you showed on the slide.

This is an agent that is not without toxicity, and it is a little bit difficult to determine what the dose/toxicity relationships are. I am assuming that the higher doses result in greater toxicity, so that presumably if one

could deliver a lower dose, you might get equivalent clinical effects with less toxicity.

So, I think it is important to try to hone in on the dosing as well as possible.

DR. SHERMAN: We have studies planned and will be opening shortly and combining gemtuzumab with chemotherapy, with standard chemotherapy, both with cytarabine and in cytarabine with daunorubicin, and in those studies we are doing dose ranging studies to look at an optimal dose of gemtuzumab in combination with chemotherapy.

DR. SCHILSKY: Another question. There is some detectable free calicheamicin in the circulation that was shown on one of the PK slides. Of course, calicheamicin is an extraordinarily potent toxin. So, I would assume that even those very low concentrations could be the cause of the liver toxicity that is seen in these studies.

Is that your presumption or what do you think is the mechanism of the liver toxicity?

DR. SHERMAN: The question relates to the amount of free calicheamicin that was measured in patients' serum and whether or not that was related to the liver toxicity. We don't have any information that the amount of free calicheamicin, which was an extremely low amount, is directly related to the liver toxicity.

There are with other antibodies, certainly

evidence that there is nonspecific hepatic clearance of the antibody, and if that does occur, there may be release of calicheamicin after nonspecific clearance of antibody with hepatocyte injury.

DR. SCHILSKY: I also am still grappling with the CRp definition. Now, according to that definition, the implication is that those patients who are the CRp patients don't have complete recovery of their platelet counts to at least 100,000, but that they are platelet transfusion independent.

I want to ask again about this definition of platelet transfusion independent. To me, as someone who doesn't treat leukemia, platelet transfusion independent means you don't need to get any platelet transfusions.

I thought I heard you say that platelet transfusion independent means that at least a week elapsed since the last platelet transfusion.

So, what is the definition of platelet transfusion independent?

DR. SHERMAN: The question relates to the definition of platelet transfusion independence in categorizing patients as CRp patients, and as written in the protocol, the definition was a period of time of one week that were platelet transfusion independent.

It is noted, though, that for all these patients

who became CRp patients, the majority of these patients did have elevations greater than 25,000. Half of them had greater than 50,000, and they tended to increase over time although did not reach the arbitrary value of 100,000 to become a complete remission.

DR. SCHILSKY: But many of them were continuing to receive platelet transfusions periodically then. No?

DR. SHERMAN: No. In clinical practice, the trigger for platelet transfusion in this setting was certainly probably about 10,000 in most of the centers.

DR. SCHILSKY: I guess what I am trying to get at is after the patient was declared to be platelet transfusion independent, that is, that they had gone a week without a platelet transfusion, how often was it that those patients subsequently required platelet transfusions, you know, were they really truly platelet transfusion independent from that point going forward?

DR. SHERMAN: The question is were these patients truly clearly transfusion independent, and they were. They received no further platelet transfusions.

DR. SCHILSKY: I think that is important. One other question along those lines. I guess I would like to address this to Dr. Appelbaum. It relates to this definition of CRp.

It does appear from the slides that you showed

that the outcome of the CRp patients was pretty similar to the outcome of the CR patients.

So, I suppose my question would be, going forward in future clinical trials in patients with acute leukemia, should the CRp category now be included along with CR because in most trials up to this point, the CRp category would have been considered partial remission.

DR. APPELBAUM: It's a good question you are asking, Rich. The problem I should say is that we have not been confronted with this previously with the kinds of chemotherapies that were used in the past, and so people have not paid as much attention to the level of platelets that you achieve.

In fact, the MRC, as I said, doesn't even include platelet recovery as part of their complete remission rate. After autologous transplants for AML, many patients do not recover to 100,000 platelets. They sit there at 60- or 70- or 80,000 platelets for a year or more, yet, we call them complete responders even though they don't quite meet the traditional definition of complete response.

We faced this issue of what to do with these CRp's. In part, it was in some of our patients a somewhat difficult decision. We treated patients, for example, with CMA-676 with the drug, and had a complete clearing of blasts, recovery of granulocytes, and the platelet count was

at 50,000 after a month, and they had an HLA matched sibling, and they were eligible to go on to a transplant.

So, we could have waited for their platelet counts to eventually get to 100,000 and call them complete responders. Was that ethical for the purposes of the study? No, because the patients, in their best interest, was to go on to a transplant once they were in complete remission.

So, they did go on before they had an opportunity to entirely recover their platelet count. I think the issue that will be interesting if this drug is brought forward--and, of course, we hope it will be--will be to ask in patients in first remission, does this preclude giving subsequent intensive consolidation chemotherapy, and if it does, it may not be a very good drug to use for initial induction in upfront AML.

It may be very good as consolidation in AML. It may be a fine drug to use in preparation for a transplant where you are getting a new source of stem cells, or it may be that in upfront AML, these people will, in fact, have much better recovery. That remains to be seen.

So, I think we have to, you know, with each new drug where we see different outcomes, I think it is important to be flexible, and not be tied in with an absolute response when 100,000 obviously is arbitrary, it's

a nice round number, and there is nothing different about 90,000 and 110,000 that any of us can think about clinically as being clinically relevant.

The patients that got a good--the CRp patients were out of the hospital, had good recovery of their granulocytes, were platelet independent as far as transfusions were concerned, so from the patient's standpoint and the physician's standpoint, when treating them, they were essentially in remission.

DR. LIPPMAN: I have two clarifications again regarding CRp. In the last part of the presentation, under Slide 8, the second bullet says CRp patients require more platelet and red blood cell transfusions.

What does that mean?

DR. SHERMAN: The question relates to the statement that patients who were CRp patients required more platelet and RBC transfusions.

DR. LIPPMAN: In relation to what Dr. Schilsky just asked, I am not sure I fully understand the CRp definition.

DR. SHERMAN: Prior to becoming a CRp patient, prior to becoming fully transfusion independent, those patients did have lower platelet counts, and so there was a longer time to recovery even to a trigger of 10,000 or to 20,000, so during that interval of time, more platelet

transfusions were given to those patients.

DR. LIPPMAN: So, it is prior to becoming CRp as opposed to CRp patients.

DR. SHERMAN: Yes, prior to achieving a CRp.

DR. LIPPMAN: The other in terms of CRp being equivalent, the slide, I think--and maybe you can put it up again--that Dr. Przepiorka asked about with the relapse-free survival of the CRp versus CR, I mean although the p-value is 0.09 with small numbers, those curves, the magnitude of the difference was substantial.

It would raise a question in my mind, given the small numbers, of whether they really are equivalent.

DR. SHERMAN: So, this question relates again to the comparison of relapse-free survival between the CR and CRp patients.

DR. LIPPMAN: Right.

DR. SHERMAN: Slide B-47.

[Slide.]

As noted, this is a Kaplan-Meier analysis and very small numbers in both groups of patients where a log-rank test did not show that there was a difference between these two curves although I think one can conclude that the numbers were too small really to detect a difference.

Overall, these patients, as judged by overall survival, had no difference, as well, too. We believe that

there are several parameters including relapse-free survival and overall survival, survival following post-transplantation that shows comparability between these two categories.

DR. LIPPMAN: I think the post-therapy obviously controls for this, but although these aren't statistically significant, it also raises a concern about how confident we are that they are not different given the shape of these curves and the small numbers.

DR. SCHILSKY: Dr. Przepiorka, do you have a follow-up on that?

DR. PRZEPIORKA: Just one. Could you just clarify - there looks to be about two people who are still alive with CRp and a lot of very early patients less than one year with CR. Is that a correct interpretation of this?

DR. SHERMAN: Yes. The events, obviously, the events here represent events, and the patients who are still alive are represented by those marks. The question related to the number of patients still being followed?

DR. PRZEPIORKA: Yes.

DR. SHERMAN: Yes.

DR. PRZEPIORKA: I just have one other question. In your NDA, you have a very nice graph of CR versus di-efflux at the time of diagnosis of relapse, and you make the statement that the CR's all occurred in patients with low

di-efflux. Do you feel that that is a generalizable conclusion?

My concern is there is a lot of patients who don't get a CR with this drug, and we don't know whether or not treatment will preclude them getting CR from what is currently standard therapy, and is there a way to hone in on the patients who would really be eligible for this treatment?

DR. SHERMAN: The question relates to the measurement of di-efflux as a measure of drug resistance in these patients, and as a part of this clinical trial, we obtained blood cells, the marrow samples for measurement of multi-drug resistance as monitored by di-efflux studies.

When these data were analyzed in an exploratory analysis, di-efflux did not correlate with outcome of either remission or overall survival. So, at this point we don't have a marker that would predict for remission outcome.

DR. SCHILSKY: We are going to take just two more questions from Drs. Berman and Albain.

DR. BERMAN: To get back to the CRp's and how they did after transplant, I think there are about seven or nine patients with CRp's who went on to get either an allo or an auto transplant. Did they require excessive platelet transfusions post-transplant? How did those patients do following transplant?

DR. SHERMAN: The question relates to the CRp patients who went on to a transplantation following their remission and whether or not they had any difference in their outcome.

We actually looked at the data in terms of their overall survival, in terms of serious adverse events, and could find no clinical difference between the outcomes of patients with CR or CRp patients following transplantation.

DR. SCHILSKY: Dr. Albain.

DR. ALBAIN: A follow-up for Dr. Appelbaum.

Fred, where would you see this agent fitting in first relapse out in practice settings given that there are other options, high-dose ara-C, for example? What algorithm might you propose given your experience, and perhaps Dr. Larson's view on this, as well?

DR. APPELBAUM: I think we need more data to be sure, but right now I don't think I would use this agent for the younger patient who had favorable cytogenetics and a long first remission and had a particularly good chance of achieving a second remission and perhaps a long second remission with really intensive consolidation chemotherapy.

So, the patient who is a favorable patient, but has no opportunity to go on to transplant, this might not be the agent that I would necessarily choose. It may be as we gain more experience that it will be fine for those

patients, but I think it is particularly advantageous in the patients where we continue to get enormous numbers of calls to provide it on a compassionate basis from our colleagues who have used it before, or for patients who we are trying to get ready for a transplant, because it is relatively nontoxic, and it's easily given, and it does not seem to-- the patients can get to the transplant without having infection and organ damage.

Secondly, in the older patient who is not well served with really intensive high-dose consolidation chemotherapy.

Those are the two places where it is the most advantageous. Whether it will prove to be better or worse in that middle ground, I think is still a question. I don't know if Dick wants to answer.

DR. LARSON: We, of course, have had a lot of discussion about this topic, and frankly, I think the two areas that Fred identified are the two most obvious targets. That is, it is a bridge to transplant, on the one hand, and secondly, for those patients who might not be able to tolerate more intensive chemotherapy because of this favorable toxicity spectrum here.

DR. SCHILSKY: For the record, that was Dr. Richard Larson.

Dr. Santana has pleaded to ask one final question.